Remarks/Arguments

Reconsideration of the above-identified application in view of the present amendment is respectfully requested. By the present amendment, claim 27 has been withdrawn. Additionally, claim 28 has been amended to recite administering an enzyme that digests protoglycan sugar wherein the enzyme digests a proteoglycan sugar selected from the group consisting of neurocan, NG2, and phosphacan.

Below is a discussion of the 35 USC 103(a) rejections of claims 1, 12-13, 17 and 23-26 and the 35 USC §112, first paragraph, rejection of claim 28.

35 USC 103(a) rejection of claims 1, 12-13, 17 and 23-26

Claims 1, 12-13, 17 and 23-26 are rejected under 35 USC 103(a) as being obvious over Fawcett et al. (Brain Research Bulletin, 199; 49(6): 377-391) in view of Kleesiek (WO 01/49831) and further in view of Jen et al. (Stem Cells 2000; 18: 307-319).

The Office Action argues that Fawcett et al. teach damage to the CNS results in the formation of glial scars (abstract) and chondroitin sulphate glycosaminoglycan (GAG) expression is increased around glial scars of CNS injury, GAG expression around glial scars inhibits axon growth, and disruption of proteoglycan synthesis has been shown to reduce inhibition of glial growth. The Office Action further argues that while Fawcett et al. do not teach using antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi constructs to inhibit XT-I or XT-II, Kleesiek teaches the cDNA of XT-I and XT-II, that XT is an initial step in the biosynthesis of the glycosaminoglycan linkage region, and making medicaments that are inhibitors of xylotransferase. The

Office Action also argues that Kleesiek does not teach using antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi constructs to inhibit XT-I or XT-II but that Jen et al. teach designing antisense oligonucleotides, ribozymes and DNAxymes. The Office Action then concludes it would be obvious to the skilled artisan to reduce GAG content in a glial scar to promote neuronal generation by inhibiting XT-I or XT-II using antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi constructs because the "use of antisense oligonucleotides are well known in the art to inhibit expression of genes by inhibiting mRNA", it seems possible to make a therapeutic inhibitor of XT-I and XT-II activity, and that all of the claimed elements were known in the prior art and one skilled in the art could have combined the claimed elements with no change in their respective function.

Claim 1 is not obvious over Fawcett et al. in view of Kleesiek and Jen et al. because: (1) Fawcett et al. in view of Kleesiek and Jen et al. do not teach or suggest to the skilled artisan that inhibiting expression or activity of XT-I and XT-II using antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi can and/or will reduce glycosaminoglycan content in a glial scar of a mammal; (2) the Office Action provides no teaching or suggestion of administering the antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi agent intrathecally, topically, or locally to the glial scar; and (3) Fawcett et al. teaches away from inhibiting expression or activity of XT-I and XT-II as a means to reduce glycosaminoglycan content in a glial scar of a mammal.

a. Fawcett et al. in view of Kleesiek and Jen et al. do not teach or suggest to the skilled artisan that inhibiting expression or activity of XT-I and XT-II using antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi can and/or will reduce glycosaminoglycan content in a glial scar of a mammal.

To establish a prima facie case of obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re* Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Fawcett et al. as noted in the Office Action, do not teach or suggest using antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi constructs to inhibit XT-I or XT-II and that the inhibition of activity or expression of XT-I or XT-II will reduce glycosaminoglycan content in a glial scar of a mammal. In fact, Fawcett et al. do not teach inhibiting any enzyme with any type of inhibitor to reduce glycosaminoglycan count in a glial scar, let alone XT-I or XT-II. Fawcett et al. provide no information to suggest that they were contemplating targeting XT. Instead, Fawcett et al. suggest targeting TGF-β with antibodies.

Kleesiek, likewise, does not teach or suggest using antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi constructs to inhibit XT-I or XT-II. Moreover, there is no teaching or suggestion in Kleesiek that administering antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi that inhibit expression of XT-I or XT-II will also reduce glycosaminoglycan content in a glial scar of a mammal.

Additionally, the most recent Office Action has provided no evidence in fact or technical reasoning that it was known at the time of the invention that the glycosaminoglycan content of a glial scar of a mammal is directly or indirectly related to the expression and/or activity of XT-I or XT-II in a subject. As noted above, the

Office Action merely states from Kleesiek that XT is an initial step enzyme in the biosynthesis of glycosaminoglycan. Kleesiek however notes that other enzymes are also involved in the production of glycosaminoglycan. Specifically, Kleesiek teaches at page 3, lines 9+ that: "The biosynthesis of glycosaminoglycans requires the coordinated action of a large number of glycotransferases." Any of these other enzymes could potentially compensate for the lost function of XT. A skilled artisan in the field of neurobiology and microbiology would recognize that it is common for there to be functional redundancy in biological systems, such that other related proteins could potentially take over the role of XT *in vivo*. For example, the functional redundancy of "isozymes", which are enzymes that perform the same function, but which are coded for by genes located at different loci called, are well known to the skilled artisan.

Kleesiek, therefore, do not teach that a glycosoaminoglycan reducing effect results from a lack of XT activity or expression. Given the well recognized complex role of glycoltransferases in the production of glycosaminoglycans in glial scars, without experiments to demonstrate that the inhibition of the expression or activity of XT is essential for reducing glycosaminoglycan content in glial scars, one skilled in the art cannot conclude that inhibiting the expression or activity of XT-I or XT-II will reduce glycosaminoglycan count in a glial scar of a mammal.

In response, the Examiner has argued that the cited art does suggest a strategy of reducing glycosaminoglycan content in a glial scar of a mammal and further argues that there is motivation to combine the teachings of Fawcett et al. with Kleesiek. On page 4 of the most recent Office Action dated May 27, 2009, the

Examiner argues that a skilled artisan, knowing that preventing synthesis of glycosaminoglycan in a glial scar can promote neural regeneration, would seek methods to inhibit glycosaminoglycan, and that a skilled artisan would also ask himself how he could inhibit GAG expression.

The Examiner further argues that Fawcett et al. makes clear that preventing synthesis of proteoglycans is a potential method of reducing glial scars and promoting axonal regeneration. However, as discussed above, Applicants maintain that while Fawcett et al. may suggest targeting proteoglycan synthesis in general to promote axon regeneration, Fawcett et al. does not make clear that inhibiting the expression or activity of XT-I or XT-II will reduce glycosaminoglycan count in a glial scar of a mammal.

The Examiner also argues that the method of claim 1 is inherently taught by Fawcett et al. in view of Kleesiek and further in view of Jen et al. since one skilled in the art would look to reduce GAG content in a glial scar to promote neuronal generation by inhibiting XT-I or XT-II using antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi constructs because the "use of antisense oligonucleotides are well known in the art to inhibit expression of genes by inhibiting mRNA". However, merely stating that inhibiting XT-1 or XT-II could potentially reduce glycosaminoglycan content in a glial scar of a mammal does not, in and of itself, provide proof that inhibiting XT-1 or XT-II results in the reduction of glycosaminoglycan and to the reduction of glial scars.

The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic.

See *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981).

To establish inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic *necessarily* flows from the teachings of the applied prior art. *Ex parte* Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990). Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. " See *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) *See also* Cont'l Can Co. USA, Inc. *v.* Monsanto Co., 948 F.2d 1264, 1268-69 (Fed. Cir. 1991) ("To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference.").

Here, the Examiner fails to provide clear and convincing evidence that inhibiting XT-1 or XT-II will necessarily lead to a reduction of glycosaminoglycan in the glial scar of a mammal, and that it would be so recognized by persons of ordinary skill. Thus, the Examiner has provided no evidence or rationale in fact or technical reasoning to show that inhibiting expression or activity of XT-I and XT-II using antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi can and/or will reduce glycosaminoglycan content in a glial scar of a mammal. As stated above, Fawcett et al. merely suggests targeting proteoglycan synthesis in general to promote axon regeneration. Such a suggestion is insufficient for establishing

inherency. Therefore, the method of claim 1 is not inherent to a person of ordinary skill in the art.

Accordingly, Fawcett et al. in view of Kleesiek, do not teach or suggest that a glycosoaminoglycan reducing effect results from a lack of XT activity or expression. Given the well recognized complex role of glycoltransferases in the production of glycosaminoglycans in glial scars, without experiments to demonstrate that the inhibition of the expression or activity of XT is essential for reducing glycosaminoglycan content in glial scars, one skilled in the art cannot conclude that inhibiting the expression or activity of XT-I or XT-II will reduce glycosaminoglycan count in a glial scar of a mammal.

Additionally, at the time of the invention, the use of antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi agent for the *in vivo* treatment of mammals was unpredictable. The Office Action provides no evidence that at the time of the invention any scientists were using or testing antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi agent *in vivo* in the neurobiology field. Jen et al. merely teach that they had some success in tissue culture but "that effective and efficient clinical translation of the antisense strategy has proven elusive" (Page 315, column 2). Furthermore, antisense technology had and still has a reputation of being unspecific and toxic. Accordingly, in contrast to the Office Action's assertion that Jen et al. make the use of any DNA enzyme or any antisense technology obvious, the skilled artisan would recognize that the use of DNA enzymes or antisense technology to inhibit expression or activity of XT-I or XT-II in a mammal is unpredictable and that it would not obvious to use antisense oligonucleotides,

ribozymes, DNA enzymes, or RNAi to XT-I or XT-II to reduce glycosaminoglycan content in a glial scar of a mammal particularly in view of Fawcett et al., Kleesiek, and Jen et al.

In the most recent Office Action, the Examiner fails to address the argument in regards to the unpredictability of *in vivo* treatments at the time of the invention. Thus, the most recent Office Action provides no evidence that at the time of the invention skilled artisans were using or testing antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi agent *in vivo* in the neurobiology field.

Applicants further contend that antisense technology had at the time of the invention, and still has, a reputation of being unspecific, toxic, and generally problematic. There remain many obstacles to successful clinical application of genetic therapies, which make antisense technology unpredictable even today. These obstacles include: (1) systemic delivery of nucleic acid may require carrier system to improve transfection efficacy and protect from nuclease degradation; (2) non-permanent correction of mRNA will necessitate readministration; (3) binding to nonspecific targets may elicit unwanted side effects; (4) antisense oligonucleotide/siRNA competitive binding to endogenous splicing machinery or miRNA pathway components; and (5) possible induction of interferon immune response to RNAi (see Wood et al., PLoS Genet. *Modulating the Expression of Disease Genes with RNA-Based Therapy*. June;3(6): e109 (2007)). The obstacles of antisense technology are further discussed in Scherer and Rossi, *Approaches for the sequence-specific knockdown of mRNA* [abstract], Nat. Biotechnol. Dec;21(12):1457-65, (2003):

> "Over the past 25 years there have been thousands of published reports describing applications of antisense nucleic acid derivatives for targeted inhibition of gene function. The major classes of antisense agents currently used by investigators for sequence-specific mRNA knockdowns are antisense oligonucleotides (ODNs), ribozymes, DNAzymes and RNA interference (RNAi). Whatever the method, the problems for effective application are remarkably similar: efficient delivery, enhanced stability, minimization of off-target effects and identification of sensitive sites in the target RNAs. These challenges have been in existence from the first attempts to use antisense research tools, and need to be met before any antisense molecule can become widely accepted as a therapeutic agent."

In contrast to the Office Action's assertion that Jen et al. make the use of any DNA enzyme or any antisense technology obvious, the skilled artisan at the time of the invention would recognize that the use of DNA enzymes or antisense technology to inhibit expression or activity of XT-I or XT-II in a mammal is unpredictable. Thus, one skilled in the art would have no reasonable expectation of success in using antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi to XT-I or XT-II to reduce glycosaminoglycan content in a glial scar of a mammal particularly in view of Fawcett et al., Kleesiek, and Jen et al. Accordingly, without a reasonable expectation of success, the method is non-obvious.

b. The Office Action provides no reasonable rationale that the cited references teach or suggest administering the antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi agent intrathecally, topically, or locally to the glial scar.

In response to the arguments put forth by the Applicants, the most recent Office Action, dated May 27, 2009, provides a conclusory statement that a skilled artisan would choose proper routes of administration based on known difficulties in

delivering drugs to neurons, and the requirement that the nucleic acid drugs listed in Jen et al. would require co-localization within the same intracellular compartments as the mRNA being targeted. The Office Action further argues, without citing specific text, that Jen et al. also discuss the issues required for RNAi, DNAzymes, Ribozymes, and antisense drugs to provide therapeutic effects, including drug delivery and localization. Based on these statements alone, the Office Action concludes that a scientifically logical rationale exists for intrathecal, topical or local administration of RNAi, DNAenzymes, Ribozymes, and antisense drugs.

Pointing out a mere discussion of the issues related to drug delivery and localization combined with a conclusory statement based solely on the Examiner's opinion, without any facts or evidence to support such a statement, does teach or suggest that the administration of antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi agent intrathecally, topically, or locally to the glial scar was known at the time of the invention and/or provide a reasonable rationale for administering the antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi agent intrathecally, topically, or locally to the glial scar. Moreover, the conclusory statement made by the Examiner is at best conjecture or speculation.

> "It is well established that a rejection based on 103 must rest upon a factual basis rather than conjecture, or speculation. Where the legal conclusion of obviousness is not supported by fact it cannot stand." *Ex parte Yamamoto*, 57 USPQ2d. 1382, 1384 (Bd. Pat. Ap. Int. 2000).

Therefore, Applicants respectfully request that the Examiner provide some basis in fact or technical literature to support its assertion that a skilled artisan would have administered the antisense oligonucleotides, ribozymes, DNA enzymes, or

RNAi agent intrathecally, topically, or locally to the glial scar or withdrawal the rejection.

c. Fawcett et al. teach away from inhibiting expression or activity of XT-I and XT-II as means to reduce glycosaminoglycan content in a glial scar of a mammal.

Claim 1 is also allowable because the skilled artisan would not look to combine the teachings of Fawcett et al. and Kleesiek because Fawcett et al. teaches away from Kleesiek. The Office Action argues that based on Fawcett et al., a skilled artisan would look for alternative (*i.e.*, non-toxic) approaches to inhibiting glial scarring caused by proteoglycal synthesis. However, based on the disclosure of Fawcett et al., a skilled artisan would not look for non-specific inhibitors of proteoglycan synthesis.

Fawcett et al. state at the second paragraph, column 2, page 384 that:

> "Another potential strategy is to target proteoglycan synthesis in general, in the way that we have used in various in vitro models using chlorates and xylosides. However, this approach has problems: one is the toxic nature, diffusibility, and lack of specificity of the reagents, the other is that heparin sulphate proteoglycan synthesis is also affected, and these molecules are promoters of axon growth and necessary for various other functions. In order for this strategy to work it will be necessary to find a means of preventing the synthesis specifically of chondroitin sulfate GAGs. " (Emphasis added)

Thus, based on the teachings of Fawcett et al. a skilled artisan would find it necessary to look for a means of specifically preventing synthesis of chondroitin sulphate GAG while not affecting heparin sulphate proteoglycan synthesis, which Fawcett et al. teach promotes axon growth and is necessary for other functions. Applicants have previously shown that the administration of DNA enzymes to a

xylotransferase reduces not only chondroitin sulphate, but also heparan sulphate production (see Brain, 2008 131(10): 2596-2605). Accordingly, a skilled artisan would not inhibit expression or activity of XT-I and XT-II as means to reduce glycosaminoglycan content in a glial scar because Fawcett et al. teach away from a non-specific glycosaminoglycan reducing method that would potentially reduce the production of promoters of axon growth, such as heparan sulphate.

The Federal Circuit has stated that teaching away is the antithesis of art suggesting that the person of ordinary skill go in the claimed direction (*In re Fine,* 837 F.2d 1071, 5 USPQ2d 1596 (Fed Cir. 1988). Applicants contend that the teaching away in Fawcett et al. from going in the claimed direction of targeting a nucleic acid sequence encoding XT-I and XT-II is a *per se* demonstration of lack of *prima facie* obviousness.

As discussed above, Fawcett et al., in view of Kleesiek, and Jen et al. fail to teach all of the limitations of claim 1, the Office Action provides no reasonable rationale that the cited references teach or suggest administering the antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi agent intrathecally, topically, or locally to the glial scar, and Fawcett et al. teach away from inhibiting expression or activity of XT-I and XT-II as means to reduce glycosaminoglycan content in a glial scar of a mammal. Accordingly, the Office Action has failed to establish a *prima facie* case of obviousness in regards to claim 1 and withdrawal of the obviousness rejection of claim 1 is respectfully requested.

Claims 12 and 13 depend from claim 1 and are therefore patentable over Fawcett et al. in view of Kleesiek and Jen et al. because of the aforementioned

deficiencies in the rejection with respect to claim 1 and the because the specific limitations recited in claims 12 and 13.

Claim 17 includes similar limitations as claim 1 and is therefore patentable over Fawcett et al. in view of Kleesiek and Jen et al. because of the aforementioned deficiencies in the rejection with respect to claim 1. Additionally, claim 17 is patentable over Fawcett et al. in view of Kleesiek and Jen et al. because the invention recited in claim 17 exhibits unexpected results.

The Court of Appeals for the Federal Circuit has stated that:

> An analysis of obviousness of a claimed combination must include consideration of the results achieved by the combination. Gillette Company *v.* S.C. Johnson & Sons, Inc., 919 F.2d 720, 16 USPQ2d 1923, (CAFC 1990)

This consideration must address objective evidence of nonobviousness. Graham v. John Deere Co., 383 US 1, 17-18, 148 USPQ 459, 467 (1966). This objective evidence can include a showing that claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would find surprising or unexpected. In re Mayne, 41 USPQ2d 1451, 1455, (CAFC, 1997).

Example 8 of the present application shows that:

> Our results indicated that XT-I DNA enzymes work *in vivo*. Administration of an XT-1 DNA enzyme decreases GAG content *in vivo*. Administration of an XT-I DNA enzyme also promotes neuronal regeneration *in vivo* following an injury to the spinal cord.
>
> A spinal cord injury was simulated in adult rats using a stab injury of the spinal cord at the C5-C6 level. The dura was opened at the C5-C6 level and a lesion was made by inserting a 25 gauge needle. Following injury, mouse dorsal root ganglia cells (DRGs) were transplanted in the C4-C5 region. The DRGs were derived from adult "green" mice. These mice express GFP under the control of the actin promoter, and thus the DRG cells are easily observable following transplantation.

> Following both injury and transplantation of DRG cells, animals were treated, at the cite of injury, with either an XT-I DNA enzyme or a control DNA enzyme. The enzyme was administered via an intratheca11y placed PE-l0 tubing connected to a P60 tubing filled with the DNA enzymes against XT-I. The tubing was connected to an osmotic minipump (Alzet). After 7 days of administration of the DNA enzyme, the animals were sacrificed and analyzed.
>
> Immunohistochemical analysis of sections through the spinal cord of these rats indicated decreased CS-56 staining in XT-I treated animals in comparison to control treated animals. Additional analysis of GFP expression demonstrated that transplanted DRG cells extended processes into and around the injury cite. Analysis of both CS-56 and GFP staining in the same section demonstrated that GAG content is decreased coincident to the regions where transplanted DRG cells migrate and extend neurites.

Moreover, the above-noted Brain 2008 abstract states:

> In the injured spinal cord, proteoglycans (PGs) within scar tissue obstruct axon growth through their glycosaminoglycan (GAG)-side chains. The formation of GAG-side chains (glycosylation) is catalysed by xylosyltransferase-1 (XT-1). Here, we knocked down XT-1 mRNA using a tailored deoxyribozyme (DNAXTas) and hypothesized that this would decrease the amount of glycosylated PGs and, consequently, promote axon growth in the adult rat spinal cord. A continuous 2-week delivery of DNAXT as near the rostral border of a peripheral nerve graft bridging the transected dorsal columns in the thoracic spinal cord resulted in an 81% decrease in XT-1 mRNA, an average of 1.4-fold reduction in GAG-side chains of chondroitin sulphate or heparan sulphate–PGs and 2.2-fold reduction in neurocan and brevican core proteins in scar tissue. Additionally, compared to control deoxyribozyme, the DNAXT as treatment resulted in a 9-fold increase in length and a 4-fold increase in density of ascending axons growing through the nerve graft and scar tissue present at the rostral spinal cord. Together our data showed that treatment with a deoxyribozyme against XT-1 mRNA decreased the amount of glycosylated PGs and promoted axon growth through scar tissue in the injured spinal cord. The deoxyribozyme approach may become a contributing factor in spinal cord repair strategies.

These results are unexpected in view of the teachings of the prior art which fail to show any evidence that inhibiting expression of XT-I can be used promote

neuronal regeneration. The most recent Office Action argues that although the references cited do not demonstrate the success achieved by the invention of claim 17, that a skilled artisan would have taken guidance from the cited art to devise a method as claimed. However, as discussed above, one skilled in the art would not have taken guidance from Fawcett et al., which teach against promoting neuronal regeneration by non-specifically reducing glycosamionglycan production, such as heparan sulphate. Therefore, the present inventions exhibits unexpected results and allowance of claim 17 is respectfully requested.

Claims 23 and 24 depend from claim 17 and are therefore patentable over Fawcett et al. in view of Kleesiek and Jen et al. because of the aforementioned deficiencies in the rejection with respect to claim 17 and the because the specific limitations recited in claims 23 and 24.

Claim 25 depends from claim 17 and further recites that a growth factor or neurotrophic factor is administered.

Claim 25 is patentable over Fawcett et al. in view of Kleesiek and Jen et al. because of the aforementioned deficiencies in the rejection with respect to claim 17.

Additionally, claim 25 is patentable over Fawcett et al. in view of Kleesiek and Jen et al. because Fawcett et al. in view of Kleesiek and Jen et al. fail to teach or suggest the administration of a growth factor or a neurotrophic factor in combination with administering the antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi agent intrathecally, topically, or locally to the glial scar.

To establish a prima facie case of obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re* Royka, 490 F.2d

981, 180 USPQ 580 (CCPA 1974). Fawcett et al. in view of Kleesiek and Jen et al. fail to teach or suggest further administering a growth factor or a neurotrophic factor. Moreover, the Office Action has failed to include any discussion or provide any teaching showing further administration of a growth factor or a neurotrophic factor. Without such a teaching or suggestion, Fawcett et al. in view of Kleesiek and Jen et al. fail to teach all of the limitations of the claimed invention and withdrawal of the rejection of claim 25 is specifically requested.

Claim 26 depends from claim 25 and further specifies the specific neutrophic factors administered to the subject. Claim 26 is patentable over Fawcett et al. in view of Kleesiek and Jen et al. because of the aforementioned deficiencies in the rejection with respect to claim 25. Additionally, claim 26 is patentable over Fawcett et al. in view of Kleesiek and Jen et al. because Fawcett et al. in view of Kleesiek and Jen et al. fail to teach or suggest the administration of the recited specific neurotrophic factors in combination with administering the antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi agent intrathecally, topically, or locally to the glial scar.

The Office Action asserts that a skilled artisan would use neurotrophic factors, such as nerve growth factor in a method of inhibiting glial scars and promoting neuronal regeneration because NGF induces the differentiation and survival of neurons and is critical for the survival and maintenance of sympathetic and sensory neurons. However, Applicants argue once again that none of the cited references teach the use of neurotrophic factors. Furthermore, none of the cited references teach the combination of the administration of neurotrophic factors with administering

the antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi agent intrathecally, topically, or locally to the glial scar. Without such a teaching or suggestion, Fawcett et al. in view of Kleesiek and Jen et al. fail to teach all of the limitations of the claimed invention and withdrawal of the rejection of claim 26 is specifically requested.

Claim 27 is hereby withdrawn from consideration per the Election dated August 31, 2006.

35 USC §112, first paragraph, rejection of claim 28

Claim 28 was rejected under U.S.C. §112, First Paragraph, as failing to comply with the written description requirement. By the present amendment claim 28 recites the method of claim 26, further comprising administering an enzyme that digests protoglycan sugar wherein the enzyme digests a proteoglycan sugar selected from the group consisting of neurocan, NG2, and phosphacan. Support for this amendment can be found on page 16 lines 10-14, page 50, line 27 to page 51, line 13 and page 86, line 27 to page 87, line 2.

The Office Action argues that claim 28 was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Office Action also argues that there is insufficient written description of the instantly claimed method comprising a genus of proteoglycan specific enzymes.

Applicant's contend that one skilled in the art at the time of the invention would have known of enzymes capable of *in vivo* proteoglycan degradation for use in the present invention. It was well known at the time of the invention, that the

enzymatic digestion of the inhibitory glycosaminoglycan (GAG) chains of extracellular matrix proteoglycans was one of several key strategies used to increase neuronal regeneration (See McKeon et al., *Exp. Neurol.* 136(1):32-43 (1995) [Abstact]; Bradbury et al., *Nature* 416(6881): 589-590(2002) [Abstract]; Pizzorusso et al., *Science* 298(5596):1248-1251 (2002) [Abstract]; and Tropea et al., *J. Neuroscience* 23(18):7034-7044, 7043(2003)). In one example known in the relevant art at the time of the invention, Chondroitinase ABC, an enzyme capable of chondroitin sulfate degradation through the cleavage of GAG side chains, was able to enzymatically modify injury-induced chondroitin sulphate proteoglycan (Bradbury et al., 2002).

In addition, on page 16, lines 10-14, the specification lists specific proteoglycan sugars (*e.g.*, neurocan, NG2, and phosphacan) which can be targeted for enzymatic degradation using well known methods in the art at the time of the invention. Therefore, based on the present amendment, the knowledge of the skilled artisan at the time of the invention and the present disclosure, the specification reasonably conveys to one skilled in the art that the inventor(s), at the time the application was filed, had possession of a method including the administration of an enzyme that digests protoglycan sugar selected from the group consisting of neurocan, NG2, and phosphacan. Accordingly, allowance of claim 28 is respectfully requested.

In view of the foregoing, it is respectfully submitted that the present application is in a condition of allowance and allowance of the present application is respectfully requested.

Please charge any deficiency or credit any overpayment in the fees for this matter to our Deposit Account No. 20-0090.

Respectfully submitted,

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